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Quantifying the Online Behavior Towards Organic Micropollutants of the EU Watchlist: The Cases of Diclofenac & the Macrolide Antibiotics

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Abstract

This study aims at quantifying and analyzing the online interest in the micropollutants Diclofenac and the Macrolide Antibiotics (Azithromycin, Clarithromycin and Erythromycin) included in the watchlist of the EU Decision 2015/495. Using online search traffic data from Google Trends, we examine the change in interest from 2004 to 2015 in five EU countries. The results show an increased Worldwide percentage change in interest in Diclofenac, Azithromycin and Clarithromycin over the selected period, in contrary to Erythromycin, that is declining. In the examined EU countries, Germany and the UK show the highest online interest with mostly increasing rates, while in France, Italy and Spain, the interest in all four substances is significantly lower.

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Keywords: Azithromycin; Big Data; Clarithromycin; Diclofenac; Erythromycin; Google Trends; Macrolide Antibiotics; Micropollutants

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1. Introduction

According to Decision 2015/495/EU [1] issued on the 20th of March, 2015, the established watchlist for the EU monitoring of Environmental Quality Standards in the field of Water Policy consists of 17 substances; 17-Alpha-ethinylestradiol, 17-Beta-estradiol Estrone, Diclofenac, 2,6-di-tetr-butyl-4-methylphenol, 2-ethylhexyl-4-methoxycinnamate, Macrolide Antibiotics (consisting of Azithromycin, Clarithromycin and Erythromycin), Methiocrab, Neonicotinoids (consisting of Imidacloprid, Thiacloprid, Thimamethoxam, Clothianidin and Acetamiprid), Oxadiazon, and Triallate.

Diclofenac, included in the EU watchlist and the 2nd most studied substance of the list over the course of the last ten years [2], is a non-steroidal anti-inflammatory and one of the most commonly used drugs [3], mostly as an analgesic, which is both orally and dermally administrated [4-5]. Diclofenac is not highly biodegradable [5] and not completely removed through biological wastewater treatment [2-3, 5-6]; in specific, Diclofenac's removal in the wastewater treatment plants (WWTPs) varies from 0%-80% [6]. This results in its detection, in high frequencies [6], in WWTP effluents [7] and in the aqueous environment [3], i.e. surface water and groundwater [6], caused mainly through human and veterinary use [4]. Diclofenac is regarded to be harmful for environmental health [2], thus its concentrations in the water environment should be monitored in order to obtain water quality [3], even though there exist no legal limits for its discharge.

The Macrolide Antibiotics, i.e. Azithromycin, Clarithromycin and Erythromycin, are antibacterial antibiotics [8] used for the treating and preventing of various infections [8-9] in humans, animals, and agriculture [8]. They have become the focus of attention, as bacteria can develop resistance to the antibiotics [8]. As the Macrolide Antibiotics cannot be fully degraded [9], they are detected in the aquatic environment: in wastewater, surface water and groundwater [8]. Even at low concentrations, they are viewed as possibly harmful to the environment [8], thus these substances require monitoring.

The micropollutants' impacts on the environment and human health need to be further evaluated [2]. Given the increasing scientific interest in micropollutants, and in order to explore the online interest in Diclofenac and the Macrolide Antibiotics included in the EU watchlist, large volumes of data and a wide variety of datasets are needed; namely Big Data. A popular tool to access these kinds of data is Google Trends [10], which is an open tool provided by Google that measures 'What's trending'. In general, online search traffic data has significant potential in improving forecastings [11] and in analyzing online interest [12]. Google Trends, as a tool for analyzing online behavior, has been highly integrated in academic research over the course of the last few years, with the validity of the Google Trends' data [13] and its contribution to forecasting [14] being widely accepted and highlighted. If the terms are carefully selected, data from Google can be useful in accurately measuring various aspects of public interest [15].

As Google Trends is becoming popular in scientific research, much focus is given in health related issues, with all the more studies integrating data from Google in their research. Previous work on the subject includes the detection of Tuberculosis outbreaks [16], the showing of the seasonality of the restless-legs symptoms [17], the examining of the change in online searches for Multiple Sclerosis [18], and the connections between online searches and dementia incidence [19]. Furthermore, Google Trends has been useful in examining the online changes in searches of keywords related to epilepsy [20] and in providing a quantitative analysis of epilepsy related searches [21]. Google Trends' data have also been used to show that the online searches in Bariatric surgery are declining [22], to explore the online interest in cancer screening examinations in the US [23], and to examine searches related to skin diseases [24], snoring [25], lung cancer [26], tobacco use [27], and flu predictions [28] and spreading [29].

As is suggested, Google Trends has the potential of becoming a valuable tool for the measurement of online interest, as it uses the revealed instead of the stated data [30], thus more accurately reflecting the public's online behavior. Our aim is to look into online searches in Google, in order to examine and quantify at first the change in the Worldwide interest in Diclofenac, Azithromycin, Clarithromycin, Erythromycin, and then in the five most populated EU countries, i.e. Germany, France, UK, Italy and Spain, over the last 12 years. The rest of the paper is structured as follows: Section 2 consists of the research methodology used to evaluate the online interest, section 3 consists of the results and discussion, and section 4 consists of the overall conclusions and further research suggestions.

2. Methodology

We use the Google Trends' [10] normalized hits' data from January 2004 to December 2015 to analyze the online interest in Diclofenac and the Macrolide Antibiotics, i.e. Azithromycin, Clarithromycin and Erythromycin, Worldwide and in the 5 most populated countries in the EU: Germany, France, UK, Italy and Spain. Data are normalized over each selected period and are downloaded online in '*.csv' format. Let D_{t_i}, A_{t_i}, C_{t_i}, and E_{t_i} be the weekly hits of the downloaded Google Trends' data for Diclofenac, Azithromycin, Clarithromycin, and Erythromycin of the i-th country, respectively. We define $D_{t_{pi}}$, $A_{t_{pi}}$, $C_{t_{pi}}$, and $E_{t_{pi}}$ as the percentized weekly hits of their respective normalized Google searches, calculated using the equations:

$$D_{t_{pi}} = \frac{D_{t_i}}{D_{t_i} + A_{t_i} + C_{t_i} + E_{t_i}} \tag{1}$$

$$A_{t_{pi}} = \frac{A_{t_i}}{D_{t_i} + A_{t_i} + C_{t_i} + E_{t_i}} \tag{2}$$

$$C_{t_{pi}} = \frac{C_{t_i}}{D_{t_i} + A_{t_i} + C_{t_i} + E_{t_i}} \tag{3}$$

$$\mathrm{E}_{\mathrm{t_{pi}}} = \frac{\mathrm{E}_{\mathrm{t_i}}}{\mathrm{D}_{\mathrm{t_i}} + \mathrm{A}_{\mathrm{t_i}} + \mathrm{C}_{\mathrm{t_i}} + \mathrm{E}_{\mathrm{t_i}}} \tag{4}$$

We proceed to calculate the yearly averages of the percentized hits and to analyze them in terms of change in interest from 2004 to 2015 in the four selected substances. The overall change from 2004 to 2015 is calculated by the formula $(x_{2015}-x_{2004})/x_{2004}$, where x denotes the respective yearly average of each region. We then perform a comparative analysis of Google searches Worldwide and the number of documents published in the Scopus database containing the terms "Diclofenac", "Azithromycin", "Clarithromycin" and "Erythromycin" in the field 'Article title'. The selected documents include 'Articles', 'Reviews', 'Letters', 'Notes', and 'Short Surveys'.

3. Results and Discussion

This section consists of the Worldwide and regional Google searches in Diclofenac, Azithromycin, Clarithromycin, and Erythromycin. The weekly hits are percentized and their yearly averages are further analyzed, in order to examine the change in online interest in the selected micropollutants, followed by a comparative analysis of the Scopus' number of documents and Google Trends hits for the examined terms.

3.1. Worldwide Interest

Figure 1 shows the Worldwide hits in Google, and Table 1 consists of the yearly averages of the Worldwide percentized hits in the terms 'Diclofenac', 'Azithromycin', 'Clarithromycin', and 'Erythromycin' from January 2004 to December 2015. Based on Figure 1, we observe that the overall online interest is higher in the term Diclofenac, with Azithromycin, Erythromycin, and Clarithromycin following in that order from 2004 to 2015.

Given the increased scientific interest in the substances and as they are suggested to be potentially harmful for environmental and human health, it would be expected that the public's online interest could be increasing as well. According to the overall change in interest from 2004 to 2015, the Worldwide interest (Table 1) is highly increasing in Azithromycin, moderately increasing in Clarithromycin and Diclofenac, and shows a high decline in interest in the term 'Erythromycin'.

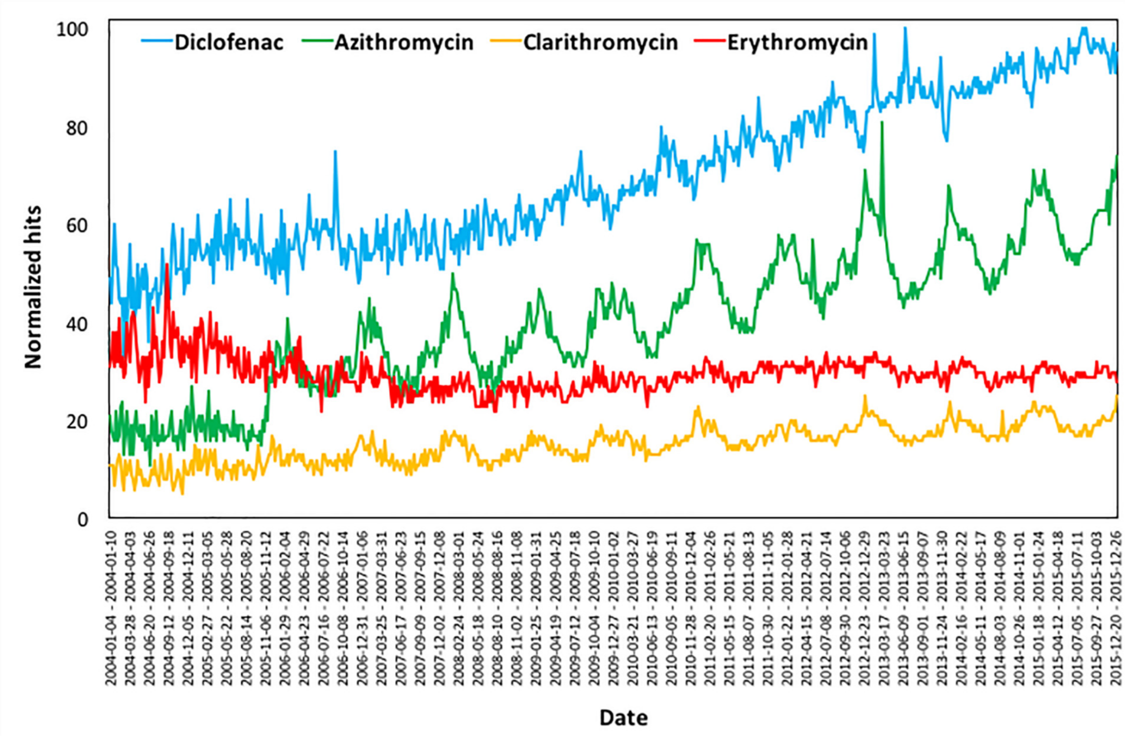

Fig 1. Worldwide hits in 'Diclofenac', 'Azithromycin', 'Clarithromycin' & 'Erythromycin' from 2004 to 2015

Table 1. Yearly averages of the percentized Worldwide hits from 2004 to 2015.

Year	Diclofenac	Azithromycin	Clarithromycin	Erythromycin
2004	43.85	16.28	8.45	31.42
2005	46.61	16.31	9.29	27.78
2006	43.90	23.83	9.45	22.82
2007	43.64	25.61	9.76	20.99
2008	44.31	26.19	10.10	19.40
2009	44.75	26.50	10.24	18.51
2010	45.13	26.59	10.02	18.26
2011	44.77	27.66	9.92	17.65
2012	44.68	28.41	9.81	17.10
2013	46.10	28.24	9.60	16.06
2014	46.23	28.70	9.79	15.28
2015	46.12	29.69	9.67	14.52
Mean annual average	45.01	25.33	9.68	19.98

3.2. Regional Interest

Figure 2 consists of the normalized hits in the terms 'Diclofenac', 'Azithromycin', 'Clarithromycin', and 'Erythromycin', in Germany, France, United Kingdom, Italy, and Spain from January 2004 to December 2015. At first glance, it is quite evident that the online interest in all four substances is higher in Germany and the UK, while in France, Italy, and Spain the interest in the examined micropollutants is lower.

Tables 2 and 3 consist of their yearly averages of the percentized hits from 2004 to 2015 in the five examined countries.

The normalized hits are percentized in order to further elaborate on the differences in online behavior towards the four substances.

Table 2. Yearly averages of the percentized hits in 'Diclofenac' and 'Azithromycn' from 2004 to 2015

	Diclofenac					**Azithromycin**				
Year	**Germany**	**France**	**UK**	**Italy**	**Spain**	**Germany**	**France**	**UK**	**Italy**	**Spain**
2004	22.55	10.26	37.11	19.84	10.25	26.72	15.75	38.60	11.48	7.46
2005	25.71	6.26	44.03	17.13	6.87	25.57	8.57	30.82	13.03	22.01
2006	29.68	5.13	46.11	12.89	6.19	24.96	8.94	31.55	22.60	11.95
2007	33.42	4.03	45.99	12.38	4.18	31.17	11.03	34.37	14.09	9.34
2008	36.53	4.55	42.27	11.81	4.84	32.98	7.08	36.54	12.22	11.17
2009	35.95	5.17	42.07	11.72	5.09	36.28	6.28	37.43	10.59	9.43
2010	35.24	6.24	41.70	11.28	5.54	37.15	5.94	40.60	7.90	8.41
2011	36.89	6.71	43.02	10.80	2.58	41.42	4.08	43.39	5.00	6.11
2012	39.13	8.22	38.86	11.36	2.43	43.74	4.15	43.18	3.83	5.10
2013	40.89	9.98	34.18	12.48	2.47	45.47	3.68	42.38	3.48	5.00
2014	44.03	11.09	27.36	14.64	2.86	46.02	3.79	43.01	2.97	4.21
2015	45.14	12.51	23.90	15.58	2.88	48.03	3.30	42.12	2.66	3.88
% Change	100.15	21.92	-35.59	-21.47	-71.90	79.78	-79.03	9.13	-76.80	-47.99

Based on the calculated yearly averages of the normalized hits in Diclofenac, high online interest is observed in Germany and the UK, which is increasing and declining, respectively. Italy shows a moderate interest in the term that is decreasing, while France and Spain achieve the lowest interest, with Spain's interest decreasing from 2004 to 2015.

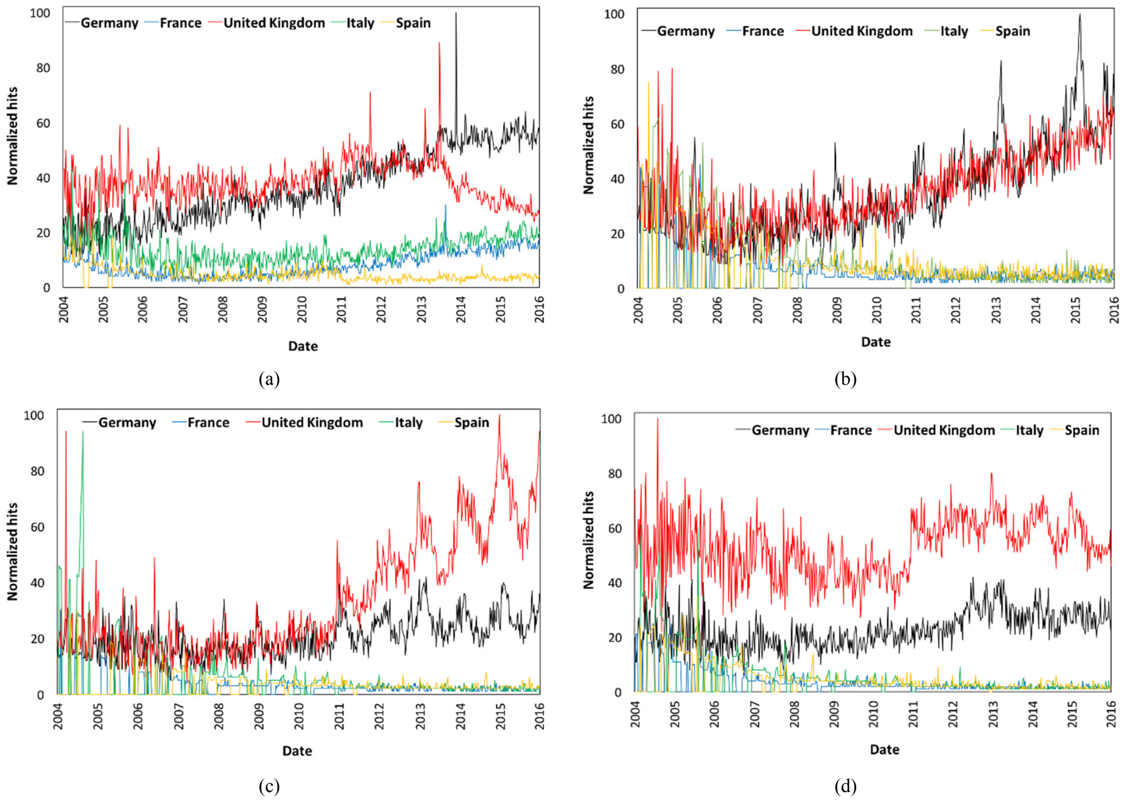

Fig. 2. Normalized hits in Germany, France, UK, Italy and Spain (a) Diclofenac; (b) Azithromycin; (c) Clarithromycin ; (d) Erythromycin for 2004-2015.

For the Macrolide Antibiotics, the interest in Azithromycin in the five selected countries is as follows: Germany and the UK show high online interest, while France, Italy and Spain show much lower interest. In Clarithromycin, high interest is observed in the UK and Germany, while low interest in the term is observed in France, Italy and Spain. In Erythromycin, UK and Germany show high interest, while France, Italy, and Spain show lower interest.

Table 3. Yearly averages of the percentized hits in 'Clarithromycin' and 'Erythromycin' from 2004 to 2015

	Clarithromycin					Erythromycin				
Year	Germany	France	UK	Italy	Spain	Germany	France	UK	Italy	Spain
2004	33.28	5.69	44.15	15.19	1.69	20.11	9.20	49.22	13.20	8.27
2005	42.10	4.80	43.37	6.64	3.09	19.69	6.74	52.70	11.16	9.71
2006	35.58	8.54	38.58	6.59	10.70	20.41	5.45	57.96	6.59	9.59
2007	36.67	5.31	39.58	9.84	8.60	21.71	4.69	61.32	7.45	4.83
2008	37.43	7.57	38.33	11.41	5.27	24.61	3.47	60.50	5.55	5.86
2009	36.42	6.23	41.07	8.44	7.85	26.05	3.79	59.66	5.73	4.75
2010	36.49	3.51	46.62	6.34	7.04	28.41	2.90	59.77	4.34	4.59
2011	34.95	3.11	53.73	4.09	4.12	25.28	1.73	67.84	2.29	2.86
2012	31.12	2.63	60.21	3.00	3.05	30.13	1.74	63.67	2.09	2.37
2013	31.19	2.22	60.91	2.56	3.12	31.12	1.83	63.75	1.51	1.80
2014	26.41	1.90	66.88	2.15	2.67	30.02	1.51	64.53	1.49	2.45
2015	26.88	1.53	67.38	1.70	2.52	31.35	1.82	63.37	1.74	1.72
% Change	-19.23	-73.16	52.60	-88.79	48.90	55.91	-80.27	28.75	-86.78	-79.19

The percentages in the regional change in interest over the examined period is as follows: Diclofenac's online interest is increasing in Germany (100.15%) and France (21.92%), and is significantly decreasing in the UK (-35.59%), Italy (-21.47%) and Spain (-71.90%). In Azithromycin, Germany's (79.78%) and UK's (9.13%) interest in the term are increasing, while France (-79.03%), Italy (-76.80%) and Spain (-47.99%) show a high decrease. In Clarithromycin, the only country with an increased online interest is the UK (52.60%) –Spain's high increase in percentage difference is due to an increase from 1.69% to 2.52%. Finally, the interest in the term Erythromycin is increasing in Germany (55.91%) and the UK (28.75%), with France (-80.27%), Italy (-86.78%) and Spain (-79.19%) showing a significantly high decrease.

3.3. Research publications for the examined substances

Over the course of the last 12 years, several studies have been dedicated to examining the micropollutants' occurrence and removal [2] and their impact on the environment and human health. Directive 2000/60/EC is the first one related to Water Policy in the EU, opening the discussion of defining and prioritizing high risk substances [31], followed by Directive 2008/105/EC that approved 33 priority substances and their Environmental Quality Standards [32]. Directive 2013/39/EU [33] proposed a list of 45 priority substances, in addition to recommending Diclofenac, 17-Alpha-ethinylestradiol (EE2) and 17-Beta-Estradiol (E2) in the list of substances for monitoring, which was later implemented in Decision 2015/495 [1]. The most studied substances out of the ones consisting the list for monitoring are Diclofenac, the Macrolide Antibiotics (Azithromycin, Clarithromycin and Erythromycin), EE2, E2 and Estrone (E1), while for the rest of the list's substances [1] not enough research has been documented yet [2].

Table 4 consists of the last twelve years' Scopus' number of documents with Diclofenac, Macrolide Antibiotics, Azithromycin, Clarithromycin & Erythromycin in the title [34], and Figure 3 of the relative interest among the four substances for Google Trends and published papers.

Further statistical analysis, as shown in Figure 3 and Table 4, suggest that the number of scientific publications for each term is related to the terms' rankings in online interest, i.e. Diclofenac, Azithromycin, Clarithromycin, and Erythromycin in that order.

However, for Diclofenac the share of the public interest among the four substances in Google Trends is higher compared to Scopus (Z=2.7376, p<0.01), while for Clarithromycin the share of the public interest among the four substances in Google Trends is lower compared to Scopus (Z=-5.5878, p<0.001).

Table 4. Scopus published documents with the four substances in their title from 2004 to 2015

Year	Diclofenac	Azithromycin	Clarithromycin	Erythromycin
2004	176	119	118	127

2005	172	149	104	142
2006	177	92	93	118
2007	178	143	89	134
2008	204	115	98	121
2009	238	120	110	110
2010	249	116	97	95
2011	279	153	101	114
2012	270	153	108	80
2013	286	179	135	97
2014	296	202	123	95
2015	254	152	91	79
Total	2779	1693	1267	1312
Percentage share	39.41%	24.01%	17.97%	18.61%

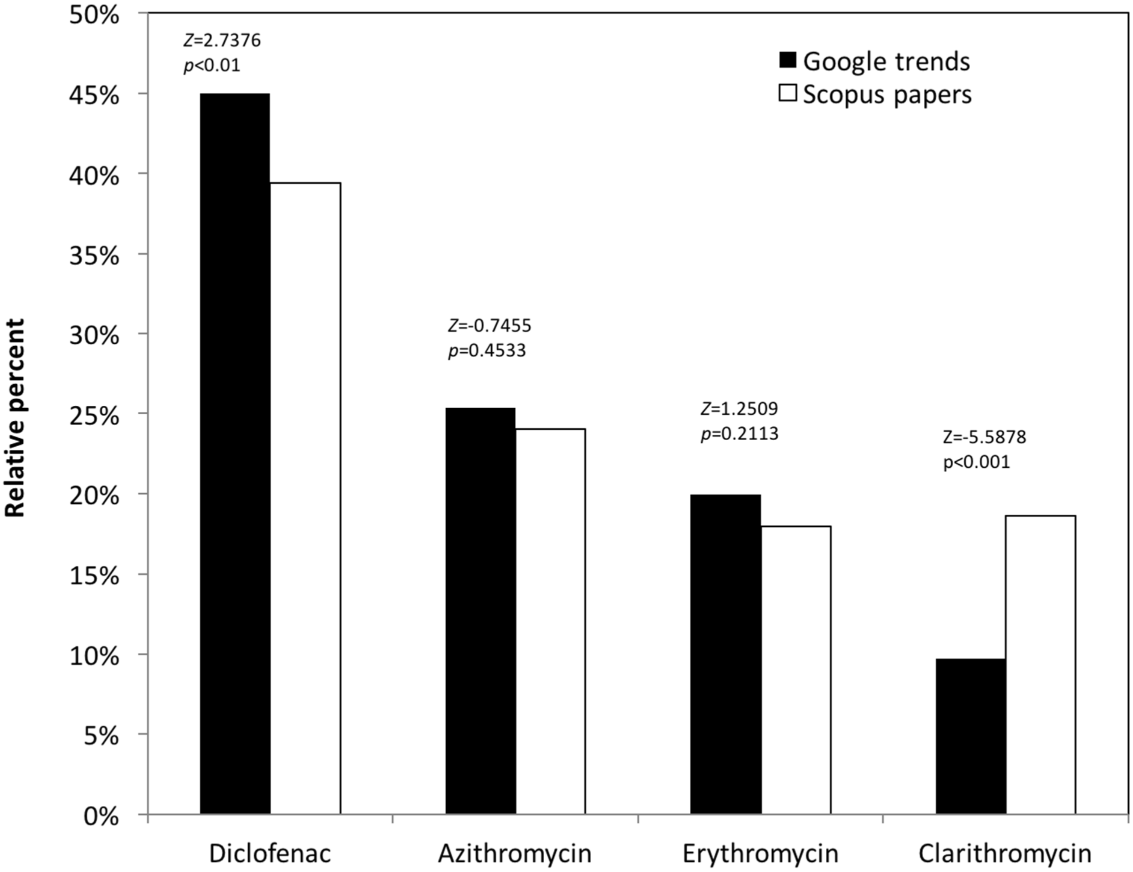

Fig. 3. Relative interest among the four substances for Google Trends and published papers in Scopus

4. Conclusions

This aim of this study was to quantify and analyze the online interest in Diclofenac and the Macrolide Antibiotics, i.e. Azithromycin, Clarithromycin, and Erythromycin, substances included in the watchlist of the EU Decision 2015/495. We used normalized data from Google Trends in order to examine the change in interest from 2004 to 2015 in Germany, France, UK, Italy and Spain. Quantifying the hits by percentizing the normalized weekly data, we observed an increased Worldwide interest in Diclofenac and Azithromycin, stable interest in Clarithromycin, and a high decrease in Erythromycin. In specific, the regional interest in Germany and UK is higher in all terms, and, in most cases, increasing, compared to France, Italy, and Spain. The percentage differences show that in Germany the interest in all substances except for Clarithromycin is increasing, and in the UK the interest in Diclofenac is decreasing, while searches in the Macrolide Antibiotics are increasing. In France the overall interest in all substances apart from Diclofenac is significantly decreasing, the same as in Italy and Spain, where the interest in all terms is significantly decreasing. In addition, both the scientific community (in terms of published papers) and the public are interested on the examined substances in the same order, i.e. Diclofenac, Azithromycin, Clarithromycin, and Erythromycin.

Google Trends is suggested to be a valid tool for evaluating online interest, as it uses the public's revealed and not the stated preferences. Data from Google Trends have been used in a high number of studies in health related issues, aiming at examining the overall increases or declines in interest in several medical terms. Further research on the subject could include the exploring of the online interest in all EU countries, in addition to the examining of the countries' interest in relation to their GDP per capita and their respective Health Care Systems' performance.

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